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### **Human T cell leukemia/lymphoma virus type I DNA and polymyositis/dermatomyositis: comment on the article by Sherman et al**

#### *To the Editor:*

In their recent article, Sherman et al showed an association between human T cell leukemia/lymphoma virus type I (HTLV-I) and polymyositis in patients from Jamaica, an endemic area for HTLV-I infection (1). The case of their patient MR was of great interest because he had negative serologic results for HTLV-I.

We have previously reported the case of a female polymyositis/dermatomyositis patient from France who was HTLV-I seronegative but in whom HTLV-I DNA sequences were detected in peripheral blood lymphocytes, by gene amplification utilizing the polymerase chain reaction (PCR) assay (2). The search for a possible HTLV-I infection in this patient was prompted by the presence of certain unusual features which have been previously noted in HTLV-I-seropositive patients. She had an intense CD8+ lymphocytic alveolitis, a pulmonary manifestation observed in patients with HTLV-I-associated myelopathy (3). She also reported xerostomia and xerophthalmia. Findings of a Schirmer's test were positive, and rose bengal staining of the conjunctiva was abnormal. Biopsy of the minor salivary glands demonstrated an interstitial lymphoplasmacytic infiltration with dilatation of the ducts. The duct of the epithelium was atrophic, and moderate interstitial fibrosis was observed. A link between HTLV-I infection and sicca syndrome has been suggested (4). Finally, she later developed a pyramidal syndrome in which deep tendon reflexes were brisk and associated with bilateral Babinski signs, as has been noted in HTLV-I-seropositive patients with polymyositis (5). In accordance with the proposal by Sherman et al that HTLV-I may play a role in polymyositis in patients from HTLV-I-endemic areas, we would suggest performing PCR analysis for HTLV-I infection in patients from non-endemic areas who have an unusual form of dermatomyositis associated with pyramidal signs, sicca syndrome, and pulmonary lymphocytic involvement.

Louis-Jean Couderc, MD  
Maria-Pia Flammang, MD  
Isabelle Caubarrere, MD  
*Hôpital Foch*  
*Suresnes, France*  
Jean-Claude Vernant, MD  
*Hôpital la Meynard*  
*Fort de France, France*

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### **American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis: comment on the article by Felson et al**

#### *To the Editor:*

We read with great interest the article by Felson et al regarding the American College of Rheumatology (ACR) preliminary definition of improvement in rheumatoid arthritis (RA) (1). We share the authors' opinion that the topic of assessing and analyzing individual treatment response in RA clinical trials is very important. We fully agree that the use of a single measure for improvement increases the power of a trial, and that we should aim for standardization of a definition for improvement since this makes it possible to compare different trials.

In their study, Felson et al selected a definition of improvement based on 1) correspondence with rheumatologists' impressions about the improvement of "paper" patients (n = 43), 2) the most powerful discrimination between active treatment and placebo (or less active) treatment, and 3) ease of use/credibility. Although we appreciate the method used to select this definition, we would like to make some minor comments.

First, to what extent do rheumatologists' impressions of paper patients for whom only 7 variables at 2 time periods are described reflect the impressions of rheumatologists in daily clinical practice? Does the selection of paper patients "near expected thresholds for improvement (20-45% improvement in at least 3 outcomes)" not implicate bias by using a predetermined definition of improvement? Second, is the difference between placebo and active treatment identified with the improvement definition a clinically relevant difference? Is there an association with outcome measures in RA, such as radiographic progression and functional capacity? Is the measure sensitive to detect smaller differences between two active treatments?

Recently, we developed response criteria based on the Disease Activity Score, using a different approach (2). During the European League Against Rheumatism (EULAR) meeting in Amsterdam (June 1995), these re-



sponse criteria were accepted as the EULAR response criteria by the Standing Committee on International Clinical Studies including Therapeutic Trials. The 3 major differences between the ACR criteria and the EULAR criteria are as follows: 1) The EULAR response criteria are based on the capacity to discriminate between high and low disease activity in patients seen in daily clinical practice, while the ACR criteria are based on the discrimination between active drug-treated and placebo-treated patients in clinical trials (an approach that has its pros and cons) (3). 2) The EULAR response criteria combine change in disease activity with the level of disease activity reached, while the ACR criteria are based on change from baseline alone. 3) The EULAR response criteria have 3 categories (good, moderate, nonresponse), while the ACR criteria have 2 categories.

Despite these differences, both measures have been developed to determine treatment response in individuals. In the absence of a gold standard, both the ACR and the EULAR definitions of response should be used and compared in as many trials as possible. As a first step, we recently presented a comparison between these 2 response definitions in 1 double-blind clinical trial (4). Currently we are comparing the 2 approaches to defining response in several double-blind trials (5). The most useful definition will be the one that can best predict clinically relevant outcomes in RA patients, combined with the ability to differentiate between more and less effective treatments.

Anke van Gestel, MSc  
Piet van Riel, MD, PhD  
*University Hospital Nijmegen  
Nijmegen, The Netherlands*

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## Reply

*To the Editor:*

The other committee members and I appreciate the interest of Drs. van Gestel and van Riel in our article reporting the ACR preliminary definition of improvement in

RA. First, let me respond to their specific questions about the development of the definition of improvement.

In surveying rheumatologists to get their impressions of which patients improved, we chose data on the 7 ACR/EULAR core set measures presented at 2 points in time because we wanted to duplicate the trial situation in which 7 core set measures are recommended (1) and in which 2 points in time (the beginning and end of trial) may be used to define whether a patient has improved. Giving physicians information on multiple time points may lead them to decide on improvement based on the time course of changes, rather than actual changes per se.

Van Gestel and van Riel are not correct in assuming that we selected only patients near thresholds of improvement. We chose patients randomly from all strata in clinical trials, and therefore selected percentage improvements that were markedly different from 20-45%. Because surveys from the Outcome Measures in RA Clinical Trials conference (2) showed that improvements of ~20-45% in core set parameters corresponded best with clinicians' impressions of patients having improved, we selected this range of improvement as one from which we oversampled patients in trials. Therefore, while our patients represented all experiences in trials including worsening and much greater improvement, we had more patients in the 20-45% improvement range than in others.

The ACR improvement definition incorporates all of the core set measures, and the core set measures were selected because they correlate with gold standard measures such as radiographic progression and functional capacity (1). Furthermore, the core set actually includes measures of functional capacity. Therefore, we are confident that the ACR definition of improvement correlates with both radiographic deterioration and functional status. Conversely, failure to improve is likely to portend worse functional status and radiographic deterioration. Nonetheless, both of these need to be confirmed in prospective studies.

In contrast to the assertion by van Gestel and van Riel, the ACR criteria were tested against comparative trials and effectively differentiated between effective second-line drugs in RA (see Figure 2 of ref. 3). They also have been shown in a recent published trial (4) to discriminate well between patients treated with combination therapy and those receiving single second-line drug therapy, suggesting that, with the use of the ACR improvement criteria, one can detect small but important clinical differences between effective regimens.

Van Gestel and van Riel list 3 important differences between the EULAR and the ACR definitions of improvement on which I would like to expand, and I will also list additional differences. First, the ACR improvement definition was constructed to correspond to clinicians' impressions of improvement, whereas the EULAR response criteria were constructed based on decisions about starting and stopping second-line drugs, decisions that are not always related to improvement.

Second, the ACR criteria use all 7 measures incorporated into the ACR/EULAR/WHO core set of measures for disease activity, a group of measures agreed upon by the EULAR group. Nonetheless, the EULAR response criteria use the Disease Activity Score (DAS) index, which focuses